REMARKS

I. Claim Status. Upon entry of this Amendment, claims 14, 23, 24, 33, 35 and 38 are pending.

Claim 1 has been amended in part to call for a free-end specific antibody that recognizes and binds to Aβ that is soluble in cerebrospinal fluid (CSF). Support for the amendment is found throughout the specification, e.g., at page 10, lines 12-16 and 25-36. The remaining amendments to claim 1 are meant to more clearly define the claimed free-end specific antibody, but do not change the scope of claim 1.

Claim 23 (directed to single chain antibodies) has been amended to be directed to antibody that recognizes and binds to Aβ that is soluble in cerebrospinal fluid (CSF). Support is found as set forth above for the amendment to claim 1. Claim 23 has been further amended to be in independent form by incorporating limitations of its former base claim, claim 1. Amended claim 35 and new claim 38 depend from claim 23 and specify specific embodiments of the single chain antibodies that are recited in the alternative in claim 23. Accordingly, the disclosure of each of claims 23, 35 and 38 does not go beyond the disclosure of the prior version of claim 35.

By this Amendment, no new matter has been added to the application.

II. Response to Rejections. The rejections set forth in the Office Action are summarized and addressed below.

A. Maintained Rejections Under 35 U.S.C. §103(a)

(i) The Examiner has rejected claim 14 as allegedly obvious over Saido et al., *J. Biol. Chem.* 269:15253-15257 (1994) ("Saido") in view of Takeda Chem. Industries Ltd., EP 0 683 234 A1 ("Takeda") and Goding, Monoclonal Antibodies, Academic Press Inc., London pp. 56-97 (1983) ("Goding"). The Examiner's contends that Saido's polyclonal antibody 9204 is specific for the free N-terminus of Aβ and that it would have been obvious to modify Saido's antibody to arrive at the antibody called for in claim 14 because Takeda teaches that antibodies specific for the N- and C-termini are useful for detection of Aβ species in vitro and that Aβ1-40 is water soluble and

further because of the general desirability of making monoclonal antibodies, such methods for making monoclonal antibodies being provided by Goding. The rejection is not well founded Saido fails to disclose an antibody as called for in claim 14 and there would have been no motivation to modify the antibody disclosed in Saido to arrive at the antibody called for in claim.

It is noted at the outset that the Examiner's position is that the former version of claim 1 did not require that the antibody bind to soluble Aβ. In response, the claims have been amended to clarify that the claimed antibodies bind to Aβ peptide that is soluble in CSF. Thus, claim 1 is directed to a monoclonal antibody that binds specifically to a free N-terminus of an amyloid β-peptide that is soluble in CSF or to a free C-terminus of amyloid β-peptide Aβ1-40 that is soluble in CSF and does not bind to the amyloid β-precursor protein from which said amyloid β-peptide may be proteolytically derived. Saido does not disclose that polyclonal antibody 9204 specifically binds the free-amino terminus of Aβ that is soluble in CSF. To the contrary, Saido discloses only that antibody 9204 binds to Aβ that in Western blotting experiments, i.e., bound to nitrocellulose (Fig. 1, 2 and 4) and Aβ that is present in fixed sections (Fig. 3). There is no doubt that Aβ bound to nitrocellulose or present in fixed sections is not Aβ soluble in CSF. Moreover, in view of the denatured and fixed and/or bound state of the Aβ that is present in the Western blotting experiments and in the sections, there is no expectation that the Aβ recognized in these experiments has a structure similar to Aβ that is soluble in CSF. Thus, an observation that antibody 9204 binds to Aβ in Western blotting experiments and in fixed sections does not support a conclusion that antibody 9204 binds to Aβ that is soluble in CSF.

Moreover, the Examiner's position that Saido teaches that "binding of antibody 9204 to APP-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or by AEFRHC" demonstrates that antibody 9204 binds to the N-terminus of Aβ soluble in CSF but does not bind to APP. These results only demonstrate that antibody 9204 is inhibited by the DAEFRC peptide. This result is to be expected, since antibody 9204 was raised against this peptide. This result does not establish that antibody 9204 binds to Aβ peptide. Furthermore, Saido performs the peptide-competition in Western blotting experiments. There is no suggestion that the antibody 9204 would bind even the haptenic peptide in CSF. In short, the conditions used to establish the binding

specificity of antibody 9204 failed to disclose that antibody 9204 bound Aβ in general (having only shown inhibition with a short, haptenic peptide) and failed in particular to show that antibody 9204 bound Aβ that is soluble in CSF (having shown only binding in Western blotting experiments). In view of these failures, one skilled in the art could not reasonably be expected to infer that antibody 9204 binds a free amino terminal end of Aβ or the free carboxy terminal end of Aβ1-40 that is soluble in CSF.

Nor does Saido provide any suggestion to obtain or choose an antibody that is free-end specific for Aβ that is soluble in CSF. Saido is directed entirely to using antibodies as diagnostic tools in vitro as probes in Western blotting or in the staining of tissue sections, wherein Aβ peptides are fixed to a solid substrate. Thus, Saido provides no hint or suggestion nor that there would have been any benefit to obtaining a free end specific antibody that binds Aβ that is soluble in CSF, as called for in claim 14.

Nor does Takeda provide any suggestion that would have led those skilled in the art to modify antibody 9204 such that it binds Aβ that is soluble in CSF. The Examiner states that Takeda teaches that certain monoclonal antibodies are specific for the N- and C-termini of Aβ are useful for the detection of Aβ1-40 and Aβ1-42 for the detection of Aβ species in vitro and that Takeda teaches that Aβ1-40 is water soluble. There is no nexus, however, between the fact that Aβ1-40 may be water soluble and the use of antibodies as diagnostic tools in vitro that would suggest modifying antibody 9204 to arrive at an antibody that binds Aβ that is soluble in CFS, as called for in claim 14. As set forth above, Saido demonstrates that Aβ antibodies that bind Aβ bound to nitrocellulose and in fixed sections are perfectly suitable for use as diagnostic tools. In short, Takeda's disclosure that Aβ1-40 is soluble adds nothing to Saido, because neither Takeda nor Saido, nor any knowledge common to those of ordinary skill provides any suggestion or appreciation that it would be desirable to modify antibody 9204 such that it binds to soluble Aβ. For at least this reason, Takeda fails to cure the defects in Saido. Thus, claim 14 is not obvious over Saido in view of Takeda.

Nor does Goding cure the defects in Saido, either alone or in combination with Takeda. The Examiner cites Goding as teaching routine methods of making monoclonal antibodies

and for the motivation to make monoclonal antibodies to decrease the lot to lot variability that can result with polyclonal antisera. The Examiner cites nothing in Goding that would suggest modifying the polyclonal antiserum disclosed in Saido such that it is free-end specific for Aβ that is soluble in CSF. For at least this reason, claim 14 is not obvious over the combination of Saido, Takeda, and Golding, either alone or in combination.

Moreover, it would not have been prima facie obvious to obtain a monoclonal with the same specificity as Saido's polyclonal antibody 9204, because a fair reading of Saido provides no suggestion to make such an monoclonal antibody, nor provides any reasonable expectation of success that such an antibody could be obtained. Saido obtained antibody 9204 by immunizing with the Aβ hexameric peptide, DAEFRC, conjugated to keyhole limpet hemocyanin (KLH), then affinity purifying antibody 9204 on peptide immobilized on Affi-Gel 10. *See* Saido, Experimental Procedures at page 15253. Only a portion of the antibodies produced by Saido's immunization procedure would have the desired specificity for a free end N-terminus of Aβ but not bind APP. Assuming, arguendo, that antibody 9204 has such a specificity, it is because the affinity purification step leads to purification of antibody molecules with such specificity. There is no suggestion in Saido that antibodies with such a specificity account for a reasonable percentage of the total antibody induced by the immunization procedure. Thus, there is no suggestion that monoclonal antibodies could be raised with the same specificity as antibody 9204, because there is no suggestion that an appreciable number of B-cell clones would have such specificity.

Moreover, by the time Saido was published in 1994, the production of monoclonal antibodies was well established. Goding, cited by the Examiner was published in 1983, eleven years before Saido. A monograph on antibodies, Harlow et al., Antibodies: A Laboratory Manual , Cold Spring Harbor Laboratory (1988) was published six years before Saido and includes chapters entitled "Monoclonal Antibodies" (Chapter 6, pages 139-243) and "Growing Hybridomas" (Chapter 7, pages 245-281). Thus, there can be no doubt that Saido was aware of methods of making monoclonal antibodies and the alleged advantages of obtaining a monoclonal antibody. Yet, Saido did not use monoclonal antibodies to obtain antibody 9204. To the contrary, Saido developed his asserted method of producing for proteolytic product-specific antibodies as early as 1992 (*See* Saido at page 15284, "Results," referencing Saido et al. 1992, 1993a and 1993b) and in the reference cited

by the Examiner states the method of developing product-specific polyclonal antibodies is a "unique methodology." *Id.* There can be no reasonable expectation that the results obtained with such a "unique methodology" could have been obtained with an alternative methodology. Furthermore, the fact that Saido repeatedly rejected obtaining monoclonal antibodies in favor of the techniques that yielded polyclonal antibodies and Saido's statement that the methodology disclosed therein has "general applicability" suggests strongly that the Examiner's stated general rationale for obtaining a monoclonal antibody with same characteristics as antibody 9204 (i.e., reduce lot to lot variability, large quantities, etc.) are not sufficient to suggest discarding Saido's "unique methodology" that repeatedly gave positive results. Thus, for at least these reasons, it would not have been obvious to use monoclonal antibody technology to derive antibodies with the same specificity as Saido's antibody 9204. For this reason additionally, claim 14 is not obvious over the combination of Saido, Takeda, and Goding.

(ii) Claims 23, 24 and 35 are rejected as allegedly obvious over Saido, Takeda, and Goding, further in view of Seubert et al., U.S. Patent No. 6,114,133 ("Seubert") and Duenas et al., *Bio Techniques* 16:476-483 (1994) ("Duenas"). The rejection is traversed, on the following grounds.

As set forth immediately above, claim 14 is not obvious over the combination of Saido, Takeda, and Goding for at least the reason that these documents do not suggest a monoclonal antibody that binds specifically to a free amino terminal end of Aβ that is soluble in CSF. Prior to the present Amendment, claims 23, 24, and 35 depend on claim 14, either directly or indirectly. Claim 23 has presently been re-written in independent form, to include features of the antibody called for in claim 14 and, in parallel to the amended claim 14 presented herein, claim 23 has further been amended to call for an antibody that binds Aβ that is soluble in CSF. Thus, for at least the same reasons as claim 14, claims 23, 24, and 36 are not obvious over the combination Saido, Takeda, and Goding. The Examiner cites Seubert and Duenas simply for single chain antibodies, as called for in claim 23. Thus, neither Seubert nor Duenas, separately or in combination, provides information required to cure the defects in Saido, Takeda, and Goding. Thus, claims 23, 24 and 35 are not obvious over any combination of Saido, Takeda, Goding, Seubert and Duenas.

For at least the reasons set forth above, the pending claims are not obvious over any combination of Saido, Takeda, Goding, Seubert and Duenas. Reconsideration of the claims and withdrawal of the instant rejection is requested.

B. New Rejections

(i) Rejections under 35 U.S.C. §112, second paragraph. The indefiniteness rejections asserted by the Examiner are addressed as follows.

(a) Claims 14, 23, 24, 33 and 35. The Examiner asserts that claim 14 was indefinite because it was unclear what term the word "binds" modifies, because "said free C-terminus of soluble amyloid peptide" lacks antecedent basis, and because the metes and bounds of "soluble" cannot be ascertained. In response, without conceding the validity of the rejection, claim 14 has been amended to call for a monoclonal antibody that binds specifically to a free N-terminus of an amyloid β-peptide that is soluble in cerebrospinal fluid (CSF) or a free C-terminus of amyloid β peptide Aβ1-40 that is soluble in CSF. The amended claim is believed to clearly set out what the claimed antibody "binds" and to further set out the metes and bounds of "soluble." Claim 14 no longer recites "said free C-terminus of soluble amyloid peptide." Thus, each of the Examiner's objections to claim 14 is believed to have been addressed and overcome.

(b) Claims 23 and 35. The Examiner objected to claim 23 on the grounds that a claim to a single chain antibody cannot be a claim in accordance with a claim to a monoclonal antibody. In response, as suggested by the Examiner, claim 23 has been redrafted in independent form. The Examiner objected to claim 35 for not properly representing alternative choices of N-terminal free ends. In response, claim 35 has been amended to be directed to eliminate the alternative choices of N-terminal free ends. The bases objections to claims 23 and 35 are thus believed to have been addressed and overcome.

For the reasons set forth above, the rejections under 35 U.S.C. §112, second paragraph are believed to have been addressed and overcome. Reconsideration of the claims and withdrawal of the instant rejections is request.

(ii) Rejections Under 35 U.S.C. §103(a). The Examiner has rejected claim 14 as obvious over Takeda Chem. Industries Ltd., EP 0 683 234 A1 ("Takeda"), Saido et al., *J. Biol.*

Chem. 269:15253-15257 (1994) ("Saido A"), Saido et al., *J. Biol. Chem.* 268:25239-25243 (1993) ("Saido B") and Goding, Monoclonal Antibodies, Academic Press Inc., London pp. 56-97 (1983) ("Goding"). The rejection is not believed to be well taken, as follows. At the outset, it is noted that claim 14 has been amended to call in part for a free end specific monoclonal antibody that binds the free C-terminus of Aβ1-40 that is soluble in CSF and which does not bind APP.

As a starting point for the instant rejection, the Examiner cites Takeda's monoclonal antibody BA-27a. The Examiner concedes that BA-27a does not have the specificity called for in claim 14. As the Examiner acknowledges, BA-27a binds to Aβ1-38 and Aβ-39. Thus, BA-27a binds to Aβ species that are at least two amino acids shorter than Aβ1-40. Accordingly, BA-27a is not "specific for the C-terminus of Aβ-40," as called for in claim 14. As the Examiner further acknowledges, BA-27a also binds to Aβ1-42. Thus, there is no evidence that BA-27a has the property that it will not bind APP.

The Examiner attempts to cure the defect in Takeda by citing Saido A, Saido B and Goding, but the attempt is not well taken, for the following reason. First, there is no suggestion in Saido A and Saido B or in the state of the art generally to modify any procedure in Takeda to produce to antibodies that are free-end specific for the free-end of Aβ1-40 but do not bind APP. The Examiner correctly cites Saido A for teaching that "similar approaches [to those in Saido A] for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxy-terminal of Aβ peptides" and that Saido's "unique methodology" seems to have general applicability. The Examiner, however, fails to correctly identify the Saido's "unique methodology" that would yield a "similar approach." Thus, the "unique approach" set forth in both Saido and Saido B is a two-step approach wherein an immunization is performed with peptide conjugated to KLH to obtain a polyclonal antiserum, which is then affinity purified against peptide immobilized to Affi-Gel 10. Saido A at page 15253, "Experimental Procedures" section. Thus, the Examiner is mistaken to conclude that it would have been obvious to use the "conventional end-peptide immunization techniques of Saido A and B" with monoclonal antibody technology, because upon reading Saido A and B one of ordinary skill in the art would recognize it as the two-step approach set forth in Saido A that leads to the antibody with the desired specificity. Saido's two-step procedure is incompatible with production of monoclonal antibodies, as disclosed in Takeda. Thus,

for this reason there is no suggestion to combine Takeda with Saido A, Saido B and Goding to arrive the antibody called for in claim 14.

The Examiner further rejects claims 23 and 33 over the combination of Takeda in view of Saido A, Saido B, and Goding and further in view of Seubert and Duenas. The rejection is traversed. The Examiner cites Seubert and Duenas solely for their teaching of single chain antibodies. Accordingly, no combination of Seubert and Duenas cures the defects in the combination of Takeda with Saido A, Saido B and Goding that is set forth immediately above. Accordingly, claims 23 and 33 are not obvious over any combination of Takeda in view of Saido A, Saido B, and Goding and further in view of Seubert and Duenas.

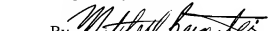
For at least the reasons set forth above, claims 14, 23 and 33 are not obvious over Takeda in view of Saido A, Saido B, and Goding and further in view of Seubert and Duenas. Reconsideration of the claims and withdrawal of the instant rejection is requested.

III. New Claim 38. Claim 38 depends from claim 23. Thus, for at least the same reasons set forth above in connection with claim 23, claim 38 is neither anticipated by nor obvious over the prior art of record. Claim 38 is further believed to comply with all requirements under sections 101 and 112. Accordingly, the Examiner is requested to allow claim 38.

IV. Conclusion. The subsisting claims are believed to be in condition for allowance and such action is earnestly solicited. If the Examiner believes there are outstanding issues that could be advanced by an Examiner's interview or an Examiner's amendment, the Examiner is invited to contact Applicant's attorney listed below.

Dated: April 3, 2007

Respectfully submitted,

By 

Mitchell Bernstein
Registration No.: 46,550
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant